

AIR FORCE INV. NO. AFD 490A  
HARVEY A. SCHWERTNER ET AL.  
SHEET 1 OF 9

BASELINE CLINICAL CHARACTERISTICS OF STUDY PARTICIPANTS*			
CHARACTERISTICS	CONTROLS (n=414)	CASES (n=138)	P VALUE
Age (years)	54.2±8.9	54.7±9.2	NS
Bilirubin (mg/dL)	0.80±0.24	0.66±0.24	<0.001
Exercise tolerance (METs)	10.2±1.9	9.3±2.0	<0.001
BMI (kg/m <sup>2</sup> )	25.6±3.0	27.1±3.8	<0.001
Fasting glucose (mmol/L)	5.7±1.0	6.0±1.3	NS
Total cholesterol (mmol/L)	5.8±0.9	5.8±1.1	NS
Triglycerides (mmol/L)	1.5±1.0	2.0±1.3	<0.001
DBP (mm Hg)	82.1±10.5	82.7±10.7	NS
SBP (mm Hg)	127.5±18.8	127.3±17.1	NS
Alcohol use (g/week)	154.9±212.8	220.1±379.3	0.010
Current smoking	14%	27%	<0.001
Previous smoking#	49%	51%	NS

\*Values are given as mean ± SD. To convert values for cholesterol and triglycerides and bilirubin to mg/dL, multiply by 38.66 and 88.54, and 0.05847, respectively.  
#The percentages of previous smoking were calculated after patients with current smoking were excluded.

*FIG. 1*

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RELATIVE RISKS AND 95% CONFIDENCE INTERVALS FOR CHD MORTALITY BY FOURTHS OF

FASTING BILIRUBIN IN MEN

	QUARTILE OF FASTING SERUM BILIRUBIN (mg/dL) ( $\mu$ mol/L)				P Trend
	1 ( $\leq 0.5$ )	2 (0.51-0.70)	3 (0.71-0.90)	4 ( $> 0.90$ )	
Cancer deaths (n=138)	50 (36%)	45 (33%)	26 (19%)	17 (12%)	
Controls (n=414)	98 (24%)	130 (31%)	103 (25%)	83 (20%)	
Crude analysis					
Relative risk	1.0	0.70	0.54	0.44	$< 0.001$
95% CI	(reference)	(0.46-1.05)	(0.34-0.87)	0.25-0.76	
Multivariate analysis*					
Relative risk	1.0	0.73	0.59	0.49	$< 0.001$
95% CI	(1.3-5.1)	(0.48-1.10)	(0.27-0.96)	0.28-0.86	

\*Adjustment for age, examination year, triglycerides, alcohol intake, previous smoking, current smoking, overweight, high cholesterol, hypertension, diabetes and low cardiorespiratory fitness.

(Dr Wei. Aren't bilirubin values in mg/dL??)

*FIG. 2*

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RELATIVE RISKS FOR CANCER MORTALITY BY EACH MG/DL INCREASE IN FASTING BILIRUBIN IN MEN

CATEGORY	Code	n	Relative risk and p-values	
			Univariate analysis	Multivariate analysis*
All-cancer mortality	140-208	138	0.27 p<0.001	0.30 p<0.001
Lung Cancer	162	35	0.10 p<0.01	0.13 p<0.01
Digestive cancer	150-159	34	0.12 p<0.01	0.12 p<0.01
Colorectal cancer	153-154	13	0.07 p<0.05	0.07 p<0.05
Prostate cancer	185	10	0.10 p=0.12	0.11 p=0.15
Bone&connective tissue cancer	170-175	9	0.27 p=0.37	0.27 p=0.38
Lymphatic&Hemotopoietic cancer	200-208	27	0.38 p=0.19	0.44 p=0.27

\*Adjustment for age, examination year, triglycerides, alcohol intake, previous smoking, current smoking, overweight, high cholesterol, hypertension, diabetes and low cardiorespiratory fitness.

*FIG. 3*

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SERUM BILIRUBIN CONCENTRATIONS OF MALES AND  
FEMALES WITH RHEUMATOID ARTHRITIS

	SEX	N	SERUM BILIRUBIN MEAN (SD) <sup>1</sup>	SERUM BILIRUBIN MEDIAN	P-VALUE	AGE
Rheumatoid arthritis <sup>2</sup>	M	25	0.62 ± 0.33	0.53	0.003	65.4 ± 9.1
Rheumatoid arthritis <sup>2</sup>	F	20	0.47 ± 0.21	0.40	0.037	57.4 ± 7.5
Rheumatology Service <sup>3</sup>	M	48	0.62 ± 0.24	0.60	0.001	53.2 ± 15.0
Rheumatology Service <sup>3</sup>	F	103	0.47 ± 0.16	0.40	0.003	55.7 ± 16.2
Rheumatoid arthritis <sup>4</sup>	M	2	0.59 ± 0.06	0.59	0.52	58.0 ± 8.5
Rheumatoid arthritis <sup>4</sup>	F	12	0.433 ± 0.13	0.40	0.017	51.0 ± 11.3
Controls	M	129	0.83 ± 0.47	0.70		32.0 ± 9.0
Controls	F	59	0.60 ± 0.40	0.60		29.4 ± 9.2
Outpatients	M	3948	0.87 ± 1.24	0.7		53.3 ± 19.1
Outpatients	F	3801	0.61 ± 0.84	0.5		53.0 ± 18.9

<sup>1</sup>Serum bilirubin concentrations are expressed as mg/dL. To convert to  $\mu$ mole/L, divide by 0.05846. <sup>2</sup>Patients with rheumatoid arthritis. <sup>3</sup>Patients receiving treatment in Rheumatology Service. <sup>4</sup>Patients from the Rheumatology Service with diagnosed rheumatoid arthritis. Bilirubin concentrations of each group were compared to controls.

*FIG. 4*

**SERUM BILIRUBIN CONCENTRATIONS OF PATIENTS WITH DIFFERENT  
FORMS OF ARTHRITIS<sup>1,2</sup>**

Type of Arthritis	N	Mean $\pm$ SD	Median	N	Mean $\pm$ SD	Median
		Females			Males	
RA	20	0.47 $\pm$ 0.21	0.40	25	0.62 $\pm$ 0.33	0.53
PSA	6	0.50 $\pm$ 0.14	0.49	7	0.64 $\pm$ 0.16	0.60
SLE	9	0.47 $\pm$ 0.16	0.46	1	0.65	0.65

<sup>1</sup>Mean alanine transaminase and aspartate transaminase activities for males and females were 26.6 and 23.7 IU/L, respectively. Normal levels are 3-55 IU/L.

<sup>2</sup>Serum bilirubin concentrations are expressed as mg/dL.

*FIG. 5*

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DAY-TO-DAY VARIATION IN SERUM BILIRUBIN  
CONCENTRATIONS OF PATIENTS WITH RHEUMATOID ARTHRITIS.

PATIENT	SEX	DATES OF ANALYSIS	N	MEAN $\pm$ SD	CV
Patient 1	Female	Jan89 - Mar89	13	0.41 $\pm$ 0.13	0.32
Patient 1	Female	Apr89-Nov89	24	0.43 $\pm$ 0.10	0.23
Patient 1	Female	Nov89 - May90	27	0.31 $\pm$ 0.14	0.45
Patient 1	Female	Jan91 - Nov91	27	0.37 $\pm$ 0.11	0.29
Patient 1	Female	Nov91 - Nov92	24	0.35 $\pm$ 0.13	0.37
Patient 2	Female	Aug91 - Dec92	15	0.23 $\pm$ 0.10	0.42
Patient 3	Male	Jan88 - Jul88	26	0.27 $\pm$ 0.10	0.38
Patient 3	Male	Sep88 - Apr90	27	0.29 $\pm$ 0.11	0.39
Patient 3	Male	Apr90 - Dec90	27	0.33 $\pm$ 0.13	0.40
Patient 3	Male	Feb91 - Nov92	26	0.53 $\pm$ 0.17	0.31

*FIG. 6*

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DAY-TO-DAY VARIATION IN SERUM BILIRUBIN  
CONCENTRATIONS OF PATIENTS WITH RHEUMATOID ARTHRITIS

Patient 1 Jan89-Mar89 Female	Patient 1 Nov89-May90 Female	Patient 1 Jan91-Nov91 Female	Patient 1 Nov91-Nov92 Female	Patient 2 Aug91-Dec92 Male	Patient 3 Jan88-Jul88 Male	Patient 3 Sep88-Apr90 Male	Patient 3 Apr90-Dec90 Male	Patient 3 Feb91-Nov92 Male
0.3	0.3	0.2	0.4	0.2	0.3	0.5	0.3	0.8
0.5	0.3	0.4	0.6	0.2	0.2	0.5	0.4	0.8
0.3	0.4	0.4	0.5	0.1	0.3	0.1	0.1	0.8
0.3	0.3	0.3	0.5	0.3	0.2	0.3	0.4	0.5
0.5	0.2	0.5	0.3	0.3	0.2	0.3	0.5	0.6
0.6	0.5	0.4	0.4	0.2	0.2	0.2	0.5	0.7
0.3	0.2	0.3	0.2	0.3	0.5	0.3	0.3	0.6
0.5	0.5	0.3	0.4	0.3	0.3	0.2	0.4	0.4
0.3	0.3	0.3	0.4	0.2	0.2	0.3	0.2	0.5
0.2	0.3	0.3	0.4	0.2	0.3	0.1	0.4	0.5
0.5	0.1	0.5	0.4	0.5	0.5	0.5	0.4	0.5
0.4	0.5	0.3	0.4	0.2	0.2	0.2	0.1	0.7
0.6	0.2	0.4	0.3	0.1	0.2	0.3	0.3	0.5
	0.1	0.3	0.1	0.2	0.1	0.3	0.2	0.6
	0.4	0.4	0.4	0.2	0.3	0.3	0.2	0.5
	0.2	0.4	0.3		0.2	0.4	0.3	0.6
	0.5	0.4	0.4		0.2	0.2	0.4	0.3
	0.2	0.2	0.5		0.2	0.2	0.1	0.6
	0.1	0.7	0.4		0.4	0.4	0.4	0.7
	0.4	0.4	0.3		0.3	0.2	0.6	0.1
	0.2	0.2	0.3		0.3	0.5	0.3	0.5
	0.1	0.4	0.1		0.5	0.3	0.4	0.4
	0.5	0.5	0.3		0.2	0.2	0.2	0.3
	0.3	0.4	0.1		0.3	0.3	0.2	0.4
	0.4	0.3			0.3	0.3	0.5	0.4
	0.5	0.3			0.2	0.2	0.3	0.5
	0.5	0.4				0.3	0.4	
N								
13	27	27	24	15	26	27	27	26
Mean $\pm$ SD								
0.41 $\pm$ 0.13	0.32 $\pm$ 0.14	0.37 $\pm$ 0.11	0.35 $\pm$ 0.13	0.23 $\pm$ 0.10	0.27 $\pm$ 0.10	0.29 $\pm$ 0.11	0.33 $\pm$ 0.13	0.53 $\pm$ 0.17
Inter-day coefficient of variation								
0.32	0.46	0.29	0.37	0.42	0.38	0.39	0.40	0.31

FIG. 7

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BASELINE CLINICAL CHARACTERISTICS OF STUDY PARTICIPANTS*			
CHARACTERISTICS	Controls (n=839)	CASES (n=385)	P VALUE
Age (years)	51.5±10.4	52.4±9.1	NS
Bilirubin (mg/dl)	7.6±0.3	6.5±0.3	<0.001
Total cholesterol (mmol/L)	5.7±0.9	6.0±1.2	<0.001
Triglycerides (mmol/L)	1.5±1.3	1.9±1.4	<0.001
BMI (kg/m <sup>2</sup> )	25.8±3.1	26.7±3.7	<0.001
DBP (mm Hg)	81.7±9.9	85.1±12.1	<0.001
SBP (mm Hg)	124.9±15.2	130.9±19.7	<0.001
Alcohol use (g/week)	185.6±286.5	163.5±290.8	NS
Abnormal resting or exercise ECG	15%	30%	<0.001
Diabetes	7%	17%	<0.001
Current smoking	14%	21%	<0.001
Family history of cardiovascular disease	35%	35%	NS

\*Values are given as mean ± SD. To convert values for cholesterol, triglycerides, and bilirubin to mg/dL, multiply by 38.66, 88.54, and 0.05847, respectively.  
Are the bilirubin values correct or should they be 0.65 ± 0.03, etc?

*FIG. 8*



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RELATIVE RISKS AND 95% CONFIDENCE INTERVALS FOR MORTALITY BY FASTING SERUM				
BILIRUBIN IN MEN				
	QUARTILE OF FASTING SERUM BILIRUBIN (mg/dl)			
	1 ( $<0.5$ )	2 (0.5-1.0)	3 ( $>1.0$ )	p-values
All-cause deaths (n=385)	83 (21.6%)	265 (68.8%)	37 (9.6%)	
Controls (n=839)	126 (15.0%)	593 (70.7%)	120 (14.3%)	
Age and examination- year adjusted analysis*				
Relative risk	1.0	0.68	0.51	$<0.0001$
95% CI	(reference)	(0.53-0.87)	(0.35-0.77)	
Multivariate analysis†				
Relative risk	1.0	0.76	0.59	$<0.0001$
95% CI	(reference)	(0.59-0.98)	(0.40-0.87)	

\*Adjustment for age and examination year.

†Adjustment for age, examination year, parental CVD, high cholesterol, current smoking, diabetes mellitus, triglycerides, alcohol intake, hypertension, current smoking, overweight, and abnormal resting and exercise ECG.

*FIG. 9*